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10/627,211	07/25/2003	Benjamin Frydman	376462001900	4243

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EXAMINER

FEDOWITZ, MATTHEW L

ART UNIT	PAPER NUMBER
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1623

DATE MAILED: 09/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

*file*

**Office Action Summary**

Application No.

10/627,211

Applicant(s)

FRYDMAN ET AL.

Examiner

Matthew L. Fedowitz

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-33 is/are pending in the application.
- 4a) Of the above claim(s) 2 and 9 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 3-8 and 10-33 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
 Paper No(s)/Mail Date 6/13/2005.
- 4) ☐ Interview Summary (PTO-413)  
 Paper No(s)/Mail Date. \_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_.

## **DETAILED ACTION**

### ***Claim Objections***

Claim 12 is objected to because it does not end with a period. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 102***

Applicant's arguments and amendments have been fully considered. The applicant's amendments to the claims have traversed the §102(a) rejection issued in the office action dated January 12, 2005. The amended claims though do raise new reasons for rejection under §103(a) below.

### ***Claim Rejections - 35 USC § 112***

#### **I. Response to Arguments**

Applicant's arguments and amendments have been fully considered and are not found to be persuasive. Claims 1, 3-8, 10-11 and 13-18 remain rejected.

The response to the Wands analysis is unpersuasive because the applicant's claims after amendment are still drawn broadly to all porphyrins conjugated to chemotherapeutic agents. The conjugation of such compositions is, by nature, unpredictable as claimed by the applicant because the applicant is attempting to provide enablement and support for the entire porphyrin class to be linked to all of the chemotherapeutic agents by showing a single example of the conjugation of mesoporphyrin IX to doxorubicin. Still further, the applicant states that the specification provides guidance on linking porphyrins to polyamines, however, even though a

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chemotherapeutic agent may contain polyamine groups does not directly demonstrate that these compounds can be conjugated to all porphyrin compounds with success or without altering the structures of the chemotherapeutic agents. Moreover, though the applicant states that the synthesis of porphyrins is very predictable, the applicant fails to demonstrate that all of the porphyrin compounds claimed may be linked to all of the chemotherapeutic agents is predictable as a single representation of the conjugation of mesoporphyrin IX to doxorubicin as provided is not seen to provide sufficient evidence of broad spectrum conjugation and anti-cancer or anti-proliferative disease activity.

Therefore, after considering the applicant's arguments, the §112 First Paragraph Scope of Enablement Rejection has not been traversed. One approach to traversing this rejection includes submitting examples from the prior art showing a diverse group of chemotherapeutic agents conjugated to diverse porphyrin compounds. In addition, the applicant is encouraged to submit a brief and concise explanation as to how the prior art enables those compounds claimed as relating to their pharmacologic or chemical classification.

## II. New Rejection

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 19-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of tumors, does not reasonably provide enablement for the treatment of diseases characterized by uncontrolled cell proliferation or cancer generally. The

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specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 19-33 are directed to a method of treating all cancers and proliferative diseases. The term cancer is interpreted to include any and all forms of cancer that are characterized as any malignant growth or tumor caused by abnormal and uncontrolled cell division that may spread to other parts of the body through the lymphatic system or the blood stream. The phrase uncontrolled cell proliferation is interpreted to include any disease that that grows or multiplies by rapidly producing new tissue, parts, cells, or offspring or to increase or spread at a rapid rate such as solid and metastasized tumors.

In light of this, it can be asserted that in spite of the vast expenditure of human and capital resources in recent years, no one drug has been found which is effective in treating all types of cancer or uncontrolled cell proliferation diseases because it is not a simple disease, nor is it even a single disease, but a complex of a multitude of different entities, each behaving in a different way. In re Hozumi, 226 USPQ 353 (ComrPats 1985).

Moreover, the determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the factual considerations. In re Wands, 8 USPQ2d 1400 (CAFC). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.” These factors include but are not limited to:

1. The breadth of the claims;

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2. The nature of the invention;
3. The state of the prior art;
4. The level of one of ordinary skill;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The existence of working examples; and
8. The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

#### *Wands Analysis*

##### 1. The Breadth of the Claims.

The breadth of the instant claims are seen to encompass the treatment of all forms of cancer and uncontrolled cell proliferation diseases that are characterized as any malignant growth or tumor caused by abnormal and uncontrolled cell division that may spread to other parts of the body through the lymphatic system or the blood stream. As well as any disease that grows or multiplies by rapidly producing new tissue, parts, cells, or offspring or to increase or spread at a rapid rate such as solid and metastasized tumors. Moreover, the claims are seen to encompass all uncontrolled cell proliferation diseases, in the absence of some specific delineation of the proliferative diseases.

##### 2. The Nature of the Invention.

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The nature of the invention is the treatment of cancer and uncontrolled cell proliferation diseases through the use of the claimed compositions and derivatives thereof. Currently, there are no known agents that treat all cancers inclusively. In addition the claims are seen to encompass methods of treating the disorders above through the oral, subcutaneous, intraperitoneal and intravenous routes.

### 3. The State of the Prior Art.

The applicant has submitted data in the specification wherein the claimed composition of Mesoporphyrin IX is conjugated with doxorubicin. However, the applicant has not submitted data, evidence or references in the prior art showing that the claimed compositions are efficacious against an adequate representation of the known forms of cancer and uncontrolled cell proliferation diseases. Furthermore, the prior art does not teach that compositions of the class claimed are effective against all forms of cancer and proliferative diseases.

The prior art teach that porphyrin compounds collect in tumors and that the chemotherapeutic agents listed have anti-cancer properties. However, the prior art does not teach that would substantiate the assertion that all combinations of porphyrins and chemotherapeutic agents would be effective against cancer and uncontrolled cell proliferative diseases.

### 4. The Level of Ordinary Skill

The level of skill is that of one with a doctoral understanding of cancer therapeutics and chemical synthesis.

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#### 5. The Level of Predictability in the Art

The treatment of conditions associated with cancer or uncontrolled cell proliferative diseases are unpredictable because they occur in different regions of the body and with different cell lines and potential for metastases. Though it is known in the art that compounds with a porphyrin core will accumulate in tumors, those porphyrin core compounds are not known for the treatment of cancers such as leukemia wherein the cancerous cells are found throughout the circulatory system. As a result, it is unpredictable as to how these compounds would be able to treat cancer of this nature of uncontrolled cell proliferative diseases.

#### 6. The Amount of Direction Provided by the Inventor

The applicant has not demonstrated sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or reference to the same in the prior art to provide a skilled artisan with sufficient guidance to practice the instant treatment of conditions associated with cancer or uncontrolled cell proliferation diseases. For example, the applicant has only submitted an example of the treatment of DU-145 xenografts in nude mice from which those skilled in the art are supposed to extrapolate the administration of such compounds to treat various forms cancer or uncontrolled cell proliferation diseases.

#### 7. The Existence of Working Examples

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without

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undue experimentation. In re Wright, 27 USPQ2d 1510 (CAFC). The disclosure does not demonstrate sufficient evidence to support the applicant's claim to the treatment of cancer and uncontrolled cell proliferation diseases proliferative diseases. There are not seen adequate representations in the disclosure or data from references of the prior art to provide a nexus between those examples and a method of treating cancer and uncontrolled cell proliferative diseases with the claimed compositions.

8. The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure

In order for there to be a method of treating cancer and uncontrolled cell proliferation diseases generally, as claimed by the applicant, it would be necessary to show that a vast range of different types of cancers and proliferative diseases can be treated that have differing cell types, locations and potentials for metastases. Furthermore, direction, in the form of examples or art recognized correlations must be shown to determine what an effective dose may be. The references submitted do not demonstrate this. Therefore, one of ordinary skill in the art would require an undue amount of experimentation in order to determine the effective dosage to treat the multitudes of different types of cancer and uncontrolled cell proliferation diseases with combinations of the claimed compositions.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

I. Composition Claims

Claims 1, 3-8, 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al. Claims 1, 3-8, 10-12 are directed to a composition comprising a porphyrin covalently linked by a linking group to a chemotherapeutic agent wherein the chemotherapeutic agent is not a polyamine, polyamine analog, cyclic polyamine, cyclic polyamine analog, dioxonaphthoquinone, or dioxonaphthoquinone derivative.

Han (US 2002/0155999 A1) teach a porphyrin molecule and derivatives thereof conjugated to anticancer drugs. The teachings of Han are described in the office action dated January 12, 2005. Han teaches the same porphyrin derivatives as claimed by the applicant linked to anticancer agents. (see claims 1-10 and paragraphs 22-27). The applicant's claims are prima facie obvious in view of the teachings of Han.

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Han though does not teach the applicant's claims in the same format as claimed by the applicant, however, the one skilled in the art would find the differences in the teaching to be negligible.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings from Han to obtain the compositions as claimed in the instant application. All of the moieties, which are substituted in the instant application, are taught in the art, and the locations of substitution are correlative with the locations of substitutions to the porphyrin core in the art. Obviousness based on similarity of structure and functions entails motivation to make the claimed compound in expectation that compounds similar in structure will have similar properties; therefore, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new porphyrin compositions conjugated to chemotherapeutic agents. See *In re Payne*, 203 USPQ 245 (CCPA 1979).

## II. Method Claims

Claims 13-17 and 19-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al. in view of Shargel et al. Claims 13-17 and 19-33 are directed to methods of treating diseases of uncontrolled cell proliferation characterized as cancer wherein the method comprises administering a therapeutically effective amount of a porphyrin conjugated to an anticancer agent. In addition, claims 16 and 17 are directed to a method of making compositions containing a porphyrin conjugated to an anticancer agent.

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Han inherently teaches the formation of a covalent bond between the porphyrin compound and the chemotherapeutic agent wherein an amide bond forms between the porphyrin carboxyl group and the amino groups of the chemotherapeutic agent (see paragraphs 27-29).

Han also teaches the use of such compounds in the treatment of cancer (see paragraphs 6-23 and claims 17-18).

Han does not teach the oral, subcutaneous intraperitoneal or intravenous administration of such compositions. However Shargel et al does teach that chemotherapeutic compositions are typically administered orally, subcutaneously, intraperitoneally or intravenously (see page 1034).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings from Han and Shargel et al. to claim the methods of making and treating as claimed in the instant application. The similarity of the methods and compounds used therein present a motivation to claim the methods the applicant's have with an expectation that similar compounds and methods will provide a similar outcome. Therefore, one of ordinary skill in the art would be motivated to claim the methods that the applicant has in attempting to claim new means of using porphyrin compositions wherein porphyrin compounds are conjugated with chemotherapeutic agents to treat cancer or proliferative diseases.

### *Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

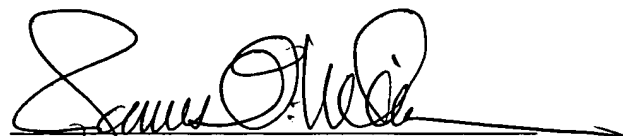
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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew L. Fedowitz whose telephone number is (571) 272-3105. If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, James O. Wilson, can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Matthew L. Fedowitz, Pharm.D., Esq.  
James O. Wilson, Supervisory Patent Examiner  
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